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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to an oral sustained release pharmaceutical preparation. More particularly, this invention is concerned with an oral sustained release pharmaceutical preparation which is prepared as a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and active drugs, or a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and active drugs together with a foaming agent, so that it may release the active drugs by such slow degrees in the stomach or the intestinal tract as to make it possible to provide an adequate supply of active drugs in enough concentration to display their therapeutic value for many hours.

2. Description of the Related Art

Various proposals have hitherto been made as to so-called sustained release pharmaceutical preparations which are made to sustain the release of the active drugs from the pharmaceutical preparations so that the efficacy of the active drugs may be maintained for many hours.

For instance, Japanese Patent Publication No. 13092/'62 gives a description of a sustained release pharmaceutical preparation of oral type comprising an active drug and slightly soluble acidic carboxyvinyl polymer and Japanese Patent Publication No. 17324/'67 carries a description of a granule and a tablet which comprise a mixture of such a hydrophilic resin as polyvinyl alcohol and polyacrylic acid and a drug and display sustained efficacy in the stomach or the intestinal tract. All of these pharmaceutical preparations are made to hold and display the sustained curative power of their active drugs in the stomach or the intestinal tract. There is, however, a probability that, granting it to be true that these sustained release pharmaceutical preparations have the property of releasing the drugs from the preparations continuously for many hours, the preparation themselves pass the site of absorption or action for the drug before the drug is released from the preparation in the body. In such a case, this most advantageous property of the preparation can not be utilized.

Another attempt is also proposed to prolong the residence time of the preparation in the stomach while allowing the preparation to release the drug in the stomach for a long time, thus keeping the effective blood concentration for many hours.

Examples of this sort might be quoted from Japanese Laid-Open Patent publication No. 61323/'74 which describes a preparation comprising a core drug coated with a polymer film which has a property of swelling in gastric juice to prevent the preparation from passing through the pylorus because of its increased mechanical bulkiness, thus prolonging its residence time in the stomach; followed up by another patent, Japanese Laid-Open Patent Publication No. 115910/'76, which contains a description of a preparation which is designed to release the drug through a hydrogel while being made to float in gastric juice by use of a large amount of fatty substance of low specific gravity.

Though these pharmaceutical preparations mentioned above are intended to release the active drugs in the stomach gradually, they involve a good possibility of allowing themselves to move on to the intestinal tract before the release of the drugs is completed due to such physiological factors as meal, stress, condition of a disease or external causes.

Japanese Laid-Open Patent Publication No. 121418/'75 describes a pharmaceutical preparation which consists of a hollow material such as foamed polystyrol, hard gelatin capsule, and expanded grain, having a coating formed thereupon and another coating of the drug applied thereon, to make them float and stay in gastric juice. The preparations of this type have a disadvantage of requiring a complicated production process.

Japanese Laid-Open Patent Publication No. 76418/'77 gives a description of a pharmaceutical preparation which is coated with a foaming agent mainly comprising bicarbonate by use of a coating material containing the drug, or is coated with a mixture of a foaming agent and the drug by use of an ordinary plain coating material so that the preparation may float in gastric juice while slowly releasing the drug; however, the preparation of this type has a demerit of having not enough sustained release effect.

On the other hand, Japanese Laid-Open Patent Publication No. 41320/'79 and Japanese Laid-Open Patent Publication No. 118414/'80 disclose a sustained release pharmaceutical preparation of oral mucosal adhesion type which comprises lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically

acceptable salt, and drug. This sustained release pharmaceutical preparation has its site of application mainly in the oral cavity and no investigation has yet been made as to its oral administration use.

SUMMARY OF THE INVENTION

It is therefore an object of this invention to provide an oral sustained release pharmaceutical preparation which releases the active drug gradually in the stomach or the intestinal tract after it is orally administered so that the active drug might be supplied in sufficient concentration for achieving satisfactory therapeutic value for an extended period of time.

It is another object of this invention to provide an oral sustained release pharmaceutical preparation whose residence time in the stomach is remarkably increased.

It is yet another object of this invention to provide an oral sustained release pharmaceutical preparation which is prepared in the form of a pilule having a specific particle size.

Another object of this invention is to provide an oral sustained release pharmaceutical preparation which can be prepared through a very simple procedure.

A further object of this invention is to provide a process for producing an oral sustained release pharmaceutical preparation.

Still another object of this invention is to provide various uses for sustained release pharmaceutical preparations.

According to the present invention, there is provided an oral sustained release pharmaceutical preparation, which comprises, in admixture lower alkyl ether of cellulose, polyacrylic acid or a pharmaceutically acceptable salt thereof, a drug and a defined amount of an effervescent foaming agent.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The lower alkyl ether of cellulose used in the present invention results from at least partial substitution of the same or different lower alkyl ether groups for a plurality of hydroxyl groups of cellulose. The lower alkyl groups in the lower alkyl ether groups may be substituted by substituents. To speak of such substituents, a hydroxyl group, for instance, may be mentioned as a preferred example.

Examples of the optionally substituted lower alkyl groups are a methyl group and hydroxy lower alkyl groups having 3 to 8 carbon atoms.

As the lower alkyl ethers of cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose, for instance, may be mentioned.

Of these mentioned above, hydroxypropyl cellulose is desirable in view of the fact that it gives an excellent sustained release effect in gastric juice to the pharmaceutical preparation made therewith.

Especially, the use of hydroxypropyl cellulose is more recommendable than any other cellulose ether. Any hydroxypropyl cellulose can be used without regard to molecular weight; however, it is preferable to use one whose 2% aqueous solution shows the viscosity ranging from 3 to 10,000 centipoises, more preferably from 1,000 to 4,000 centipoises.

As the polyacrylic acid to be used in the present invention, not only acrylic acid as a single polymer but also as a copolymer, available on the market, of acrylic acid and alkyl sucrose, methyl acrylate, methacrylic acid, methyl methacrylate, hydroxyethyl methacrylate, styrene or such vinyl ether monomer as methyl vinyl ether, whether in a single use or in a mixed use of more than one, may be mentioned.

The component mixing ratio of these copolymers may be optionally changed within such a range as to maintain water solubility or swelling property.

A mixture of polyacrylic acid and some quantity (ordinarily about 20% by weight or less) of a water soluble polymer (polymethacrylic acid or its salt, and polyethylene glycol, for instance), all available on the market, can also be used as polyacrylic acid in this invention. As a pharmaceutically acceptable salt of polyacrylic acid in the present invention, its sodium salt and potassium salt are preferable ones and its degree of neutralization is optional. Polyacrylic acid or its pharmaceutically acceptable salt can be used regardless of its molecular weight; however, it is preferable to use one whose viscosity ranges from 360 to 165,000 centipoises when it is determined at 25.0 ± 0.5°C in an aqueous solution (pH 7 to 7.5) of its sodium salt containing polyacrylic acid of 0.2% concentration. Polyacrylic acid or its pharmaceutically acceptable salt can be used singly or as a mixture of more than one kind in the present invention.

The mixing ratio between the lower alkyl ether of cellulose and the polyacrylic acid or its pharmacentically acceptable salt to be contained in the pharmaceutical preparation of this invention may preferably be 0.1 to 1,000 parts by weight of polyacrylic acid or its pharmaceutically acceptable salt to 10 parts by weight of lower alkyl ether of cellulose, more preferably be 0.1 to 10 parts by weight of polyacrylic acid or its

pharmaceutically acceptable salt to 10 parts by weight of lower alkyl ether of cellulose.

As the original drug which is involved in this invention as its active ingredient, any drugs may be used so far as they are drugs for gastrointestinal diseases and general disease therapeutic drugs which can be expected to display much more increased therapeutic value than before as the result of a sustained release effect and the following drugs may be mentioned as such ones.

(a) Drugs for gastrointestinal diseases

Drugs for peptic ulcer such as allantoin, aldioxa, pirenzepine hydrochloride, secretin, urogastrone, cetraxate, cimetidine, ranitidine, p-(trans-4-aminomethyl cyclohexylcarbonyl) phenylpropionate hydrochloiine salt, and prostaglandins; antacids such as synthetic aluminium silicate, natural aluminium silicate, dimagnesium aluminic silicate, magnesium bismuthide aluminic silicate, dehydrated aluminium hydroxide gel, hydrotalcite, magnesium aluminic metasilicate, magnesium silicate, magnesium oxide, heavy magnesium oxide, magnesium hydroxide, magnesium carbonate, and precipitated calcium carbonate; anti-pepsin drugs such as sucrose sulfuric ester, pepstatin, and streptostatin; and digestive enzymes such as pepsin, diastase, and lipase.

(b) Drugs for central nervous system

Hypnotics and sedatives such as diazepam and estazolam; antiepileptics such as phenytoin, peprobamate, and nitrazepam; antipyretic analgesics and antiphlogistics such as acetaminophen, ethenzamide, salicylamide, pentazocine, clofeson, indometacin, ketoprofen, naproxen, flurbiprofen, dichlorophenac, clidanac, alclofenac, flufenamic acid, mefenamic acid, sulinda, piroxicam, menthol, camphor, d-penicillamine, and corticosteroide; atraxics such as chloropromazine; and anti-vertigo drugs such as isoprenaline, betahistine mesylate, and scopolamine.

(c) Antiallergic agents and antihistamic agents

Diphenhydramine, cyproheptadine, etc.

(d) Drugs for circulatory system

Cardiotonics such as digitalis and ubidecarenon; antiarrhythmic agents and β-blockers such as pindolol, propranolol hydrochloride, alprenolol hydrochloride, and oxprenolol hydrochloride; diuretics such as theophylline, trichlormethiazide, spironolactone, methyclothiazide, metolazone, tripamide, furosemide, and penttutizide; antihypertensive agents such as reserpine, clonidine methyldopa, hydralazine syrosingopine, resinnamine, cinnarizine, prazosin hydrochloride, and dihydropyridine derivatives including nifedipine; capillary stabilizers such as rutin and carbazochrome; angiotonics such as dihydroergotamine mesylate and dihydroergotoxine mesylate; coronary vasodilators such as nitroglycerin, isosorbitol dinitrate, dilazep dihydrochloride, nifedipine, diltiazem hydrochloride, trimethazidine hydrochloride, trapidil, and dipyridamole, peripheral vasodilators such as inositol and hexanicotinate; drugs for arteriosclerosis such as chlofibrate; pentoxifylline, cytochrome c, dextran sulfate sodium, pyrithioxine, citicoline, nicardipine hydrochloride, dopamine hydrochloride, prostaglandins, prostacyclins, dobutamine hydrochloride, alprostadil, and ifenprodil tartrate.

(e) Drugs for respiratory diseases

Antitussives and expectorants such as ephedrine hydrochloride, codein, and bromhexine hydrochloride; isoproterenol, dextromethorphan, ipratropium bromide, and sodium cromoglicate.

(f) Hormone drugs and hormone controling drugs

Pituary gland hormone drugs such as human growth hormone, corticotropin, oxytocin, vasopressin, and protereline tartrate; male sex hormone such as testosterone; and female sex hormone such as progesteron and estradiol.

(g) Drugs for urinary and genital organs

Uterotonics such as dinoprost and dinoprost.

(h) Metabolic drugs

Vitamins such as 1α-hydroxycholecalciferol, 1,24-dihydroxycholecalciferol, and mecobalamin; nutrients, tonics, and alteratives; glutathione, ATP, aprotinin, and gabexate mesilate.

(i) Drugs for tumor

Krestin, aclarubicine hydrochloride, mitomycin C, methotrexate, carboquone, cytarabine, picibanil, 5-fluorouracil derivatives involving tegafur and carmofur.

(j) Antibiotics

Tetracycline antibiotics, penicillins, cephalosporin antibiotics, etc.

(k) Chemotherapeutic agents

Clotrimazole, pyrrolnitrin, and sulfa drugs.

Of these drugs, drugs for peptic ulcer, antacids, anti-pepsin drugs, digestive enzymes, hyponotics and sedatives, antiarrhythmic agents and β-blockers, diuretics and antiotonics are preferable, and drugs for peptic ulcer, antacids, anti-pepsin drugs, digestive enzymes and antiarrhythmic agents and β-blockers are especially preferable.

These drugs can be used singly or in a mixture of more than one provided that they are not incompatible with each other. The amount of these drugs to be used corresponds to the effective dose of the pharmaceutical preparation of this invention applied to the respective diseases and may be determined suitably depending upon the degrees of activity of the drugs, etc.

The oral sustained release pharmaceutical preparation of this invention contains a foaming agent together with the lower alkyl ether of cellulose and polyacrylic acid or its pharmaceutically acceptable salt. The foaming agent gradually starts reacting with gastric juice to generate a foam of carbon dioxide in the stomach upon the oral administration of the pharmaceutical preparation thus allowing the preparation to float and prolong its staying time in the stomach, which enhances the sustained release effect of lower alkyl ether of cellulose and polyacrylic acid or its pharmaceutically acceptable salt.

As the foaming agent to be used in this invention, there are such carbonates and bicarbonates as sodium hydrogencarbonate, sodium carbonate, potassium carbonate, and potassium hydrogencarbonate. These salts may also be used in combination with an organic acid such as citric acid, tartaric acid, succinic acid, fumaric acid, maleic acid, and ascorbic acid. With the purpose of improving the foaming property and the foam-induced dispersibility of a mixture of lower alkyl ether of cellulose and polyacrylic acid or its pharmaceutically acceptable salt, or for securing the benefit of patients with anacidity, the combined use of carbonate or bicarbonate and any of such organic acids as citric acid, tartaric acid, succinic acid, fumaric acid, maleic acid, and ascorbic acid is recommendable.

The amount of the foaming agent is an important factor in the making of the present pharmaceutical preparation since it exerts influence upon the stay of the obtained preparation in the stomach and it is necessary to use the foaming agent in an amount of 10 to 50% by weight of the total weight of lower alkyl ether of cellulose and polyacrylic acid or its pharmaceutically acceptable salt. If the amount of the foaming agent exceeds 50% by weight, the preparation will start foaming at once in the stomach immediately after its oral administration only to make the stay in the stomach undesirably short. If the amount is less than 10% by weight, the preparation will not be able to display enough sustained releasing function in the stomach. It is especially desirable to use the foaming agent in an amount of 10 to 30% by weight of the total weight of lower alkyl ether of cellulose and polyacrylic acid or its pharmaceutically acceptable salt.

To speak of the dosage form of the oral sustained release pharmaceutical preparation of this invention, it should desirably be prepared in the form a pilule such as subtilized granule and normal granule or a tablet. It is not proper to use a pilule or tablet of excessively large size, since they are expected to disintegrate and disperse and then complete releasing the drug while they pass the site of absorption. On the other hand, it is not proper either to use a pilule or tablet of excessively small size, since the increase in their total surface area promotes their disintegration and dispersion to allow the drug to be wholly released before passing the site of absorption thus reducing the effect of sustained release. It is, therefore, preferable to make the oral sustained release pharmaceutical preparation of this invention in the form of a pilule whose

particle size ranges from 0.5 to 2mm, especially ranging from 0.5 to 1.5 mm. As for the size of a tablet, it is preferable to form it measuring 2 to 8 mm in diameter and 1 to 5 mm in diameter and 1 to 5 mm in thickness, especially measuring 3 to 6 mm in diameter and 1 to 4 mm in thickness. The pilule or the tablet thus prepared may be used after having been filled in an ordinary hard capsule.

In order to improve the physical properties, appearance, or odor of the oral sustained release pharmaceutical preparation of this invention, it may, if desired, contain one or more than one known additives such as a lubricant, binder, and vehicle. As the lubricant, talc, stearic acid or its salt, and wax, for instance, may be mentioned. As the vehicle, there are starch, crystalline cellulose, dextrin, lactose, mannitol, and sorbitol.

The oral sustained release pharmaceutical preparation of this invention is prepared by thoroughly mixing the active drug with lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt and one or more foaming agents. There may be further added, if necessary, a lubricant, binder, and vehicle, followed by mixing the components up well to obtain a mixed compound, and then forming the compound into a pilule or a tablet, as case may require, according to a known method.

More particularly, for instance, the lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, foaming agent and the active drug are mixed homogeneously with the addition, if desired, of a lubricant, binder, etc. thereto. The mixed compound may be made into a pilule according to the dry granulating method and the thus obtained pilule may further be made into a tablet according to an ordinary method. The pilule or the tablet may also be filled in a hard gelatin capsule to give hard capsules.

In cases where the active drug becomes unstable upon contact with polyacrylic acid or foaming agent, the drug may be coated with any known coating agent such as hydroxypropylmethylcellulose, polyvinyl acetal diethylaminoacetate, etc. beforehand, or may be made into minor pilules along with any known vehicle such as hydroxypropylcellulose, starch, lactose, etc. that are inert to the drug before they are formed into a pilule or a tablet of the composition provided by this invention.

The following method can also be employed as another process. The lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and the active drug are first mixed homogeneously, and then, if necessary, one or more than one kind of lubricant, binder, and vehicle are added thereto and mixed thoroughly. The mixture is then subjected to dry granulating and further, if necessary, to dry classification to obtain granules of the same particle size. As for the foaming agent, it is also dry granulated singly or, if desired, in combination with a lubricant, binder, and vehicle. These two kinds of granules may be mixed together and used as they are as a granule preparation or a pilule preparation, or filled in a hard capsule for convenient administration, or further made into a tablet along with a lubricant, if necessary, according to a generally practised method.

The oral sustained release pharmaceutical preparation provided by the present invention has excellent characteristics and efficacy as mentioned below.

(1) When orally administered, the oral sustained release pharmaceutical preparation absorbs body fluid and swells, gradually releasing the drug at a controled rate. More particularly, the pharmaceutical preparation gradually starts swelling under the influence of the body fluid and the release of the drug takes place at the swollen part. The preparation can, therefore, continue to supply the site of application or the site of absorption with the drug for many hours.

(2) The sustained release pharmaceutical preparation of this invention may be regarded as a preparation endowed with an outstanding sustained release function because it is made in the form of a pilule having a specified particle size which makes it possible to continue releasing the active drug in the gastro-intestinal tract for a long period of time.

(3) The pharmaceutical preparation of this invention makes it possible to easily control the rate of releasing the active drug to meet the purpose of remedial treatment by changing the volume ratio of lower alkyl ether of cellulose to polyacrylic acid or its pharmaceutically acceptable salt.

(4) Since the process of its preparation is easy and its formation is based on the press-shaping and dry slugging and granulating method, the stability of its active drug is kept undamaged and the process itself is advantageous from the economical viewpoint.

(5) It stays floating in the stomach for a long time and accordingly its active drug can be made to work in high concentration directly and locally on the affected part in the stomach without allowing itself to pass the site of absorption or the site of action before releasing the drug.

(6) Upon absorption of gastric juice, it disperses in the state of floating granules, which then swell and release the drug gradually. To explain the state in detail, it starts forming under the influence of gastric juice acidity, thus allowing the mixture of lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and the active drug to disperse in the state of floating particles. Then the dispersed particles gradually become swollen one by one. Since the release of the active drug takes

place at the swollen part of the particle, it can keep supplying the drug to the diseased part or the site of absorption for many hours.

EXAMPLES

The present invention will now be further illustrated in detail by the following Examples, wherein "parts" are all by weight unless otherwise noted.

Example 1

It was made apparent in the following experiment that the release of the active drug from the pharmaceutical preparation of this invention was carried out gradually.

A mixture consisting of 95 parts by weight of a mixture of hydroxypropylcellulose and polyacrylic acid mixed in an uneven ratio and 5 parts by weight of riboflavin was made into granules ranging from 12 to 24 mesh in particle size according to the dry granulating method.

Apart from the above procedure, granules ranging from 12 to 24 mesh in particle size were prepared according to the dry granulating method from a mixture comprising 70 parts by weight of a mixture of hydroxypropylcellulose and polyacrylic acid mixed in an uneven ratio, 5 parts by weight of riboflavin, and 25 parts by weight of sodium hydrogencarbonate.

Another type of granules ranging from 12 to 24 mesh in particle size were made according to the dry granulating method from a mixture of 95 parts by weight of hydroxypropylcellulose or lactose and 5 parts by weight of riboflavin.

Still another type of granules ranging from 12 to 24 mesh in particle size were made according to the dry granulating method from a mixture consisting of 70 parts by weight of hydroxypropylcellulose or lactose, 25 parts by weight of sodium hydrogencarbonate, and 5 parts by weight of riboflavin.

The riboflavin dissolution test was made according to Japanese Pharmacopoeia's dissolution test method by use of 200 mg each of the specimens in the form of granule. The dissolution test was conducted according to the second method by use of 500 ml of the first solution as the specimen solution under the condition of 100 rotations.

The result is shown in Table 1 and Table 2.

Table 1

Dissolubility	Composition			
	Hidroxypropylcellulose*1 /polyacrylic acid*2/ sodium hydrogencarbonate		Hydroxypropyl-cellulose*1 /sodium hydrogen-carbonate	Lactose/ sodium hydrogen-carbonate
	59.5/10.5/25	29/21/25	70/25	70/25
Time (hr) for 50% dissolution	3.3	3.5	1.2	0.05
Time (hr) for 80% dissolution	7.5	8.0	2.3	0.15

*1 2% aqueous solution, viscosity of 2,080 centipoises, at 20°C.

*2 0.2% aqueous solution (pH 7.3), viscosity of 11,500 centipoises, at 25°C.

Table 2

Dissolubility	Composition				
	Hydroxypropylcellulose*1/ polyacrylic acid*2			Hydroxypropylcellulose*1	Lactose
	85/15	70/30	50/50	100	100
Time (hr) for 50% dissolution	2.3	2.4	1.3	1.2	0.05
Time (hr) for 80% dissolution	4.7	5.5	2.3	2.0	0.17

*1 2% aqueous solution, viscosity of 2,080 centipoises, at 20°C.

*2 0.2% aqueous solution (pH 7.3), viscosity of 11,500 centipoises, at 25°C.

It is apparent from Table 1 and Table 2 that the mixture of hydroxypropylcellulose and polyacrylic acid shows the sustained release and the dissolution time varies depending upon the mixing ratio. In case where the mixture contains sodium hydrogencarbonate, the granular composition dispersed and floated and the dissolution time was further extended. No floating was found with the granular composition which did not contain a foaming agent.

Example 2

85 parts by weight of hydroxypropylcellulose (viscosity of 2% aqueous solution at 20°C being 2080 centipoises), 15 parts by weight of polyacrylic acid (viscosity of 0.2% aqueous solution of pH 7.3 at 25°C being 11,500 centipoises), 2 parts by weight of dyestuff (amaranth), and 50 parts by weight of sodium hydrogencarbonate were mixed homogeneously. The mixture was dry granulated into granules ranging from 20 to 24 mesh (0.70 mm to 0.84 mm) in particle size. 150 mg of thus prepared granule was filled in No. 2 capsule, which was then inspected with the use of Japanese Pharmacopeia's dissolution tester (No. 2 method, 1st solution 500 ml, 100 rpm). It was observed that the capsule case dissolved and disappeared in 10 minutes or so allowing the freed granules to disperse and float on the test solution. It was further confirmed that the granules kept dispersing and floating even 12 hours after that.

Of the granule prepared in the above, 10 pieces were filled in a mini-hard gelatine capsule and given to a rat. Eight hours later, the rat was subjected to laparatomy and it was confirmed that the dyestuff (amaranth) still remained there to show the long stay of the granule in the stomach.

Example 3

A powdery mixture was prepared by evenly mixing 85 parts by weight of hydroxypropylcellulose (viscosity of 2% aqueous solution at 20°C being 2,080 centipoises) and 15 parts by weight of polyacrylic

acid (viscosity of 0.2% aqueous solution pH 7.3 at 25°C being 11,500 centipoises). A prescribed amount of sodium hydrogencarbonate powder was added thereto and mixed thoroughly. The mixture was then dry granulated into granules ranging 12 to 24 mesh in particle size. 150 mg of thus obtained granule was filled in a hard capsule and put to Japanese Pharmacopeia's dissolution tester (No. 2 method, 1st solution 500 ml, 100 rpm) to check the dispersing and floating conditions in 4 hours. The result is shown in Table 3.

Table 3

Ratio of hydroxypropylcellulose/ polyacrylic acid (85/15) to sodium hydrogencarbonate	Result		
	Dispersion or coagulation	Suspension or sedimentation	Time of suspension (hr)
30 / 70	Dispersion	Suspension	0.5
40 / 60	Dispersion	Suspension	0.8
50 / 50	Dispersion	Suspension	2.5
60 / 40	Dispersion	Suspension	3.5
70 / 30	Dispersion	Suspension	8.0
80 / 20	Dispersion	Suspension	8.5
90 / 10	Dispersion	Suspension	7.0
100 / 0	Coagulation	Sedimentation	-

As seen from Table 3, the use (10 ~ 50%) of sodium hydrogencarbonate as the foaming agent proved effective for securing dispersion and suspension.

Example 4

70 parts by weight of hydroxypropylcellulose (viscosity of 2% aqueous solution at 20°C being 2,080 centipoises), 30 parts by weight of polyacrylic acid (viscosity of 0.2% aqueous solution pH 7.3 at 25°C being 11,500 centipoises), and 2 parts by weight of dyestuff (amaranth) were mixed evenly and dry granulated into a granular substance ranging from 12 to 24 mesh (0.71 mm to 1.41 mm) in particle size (hereunder referred to as granular substance (A)).

Separately, 60 parts by weight of sodium hydrogencarbonate and 40 parts by weight of citric acid were mixed well and dry granulated into a granular substance ranging from 16 to 24 mesh (0.71 mm to 1.00 mm) in particle size (hereunder referred to as granular substance (B)).

Thereafter, 70 parts by weight of granular substance (A), 30 parts by weight of granular substance (B), and 0.5 part by weight of magnesium stearate were mixed thoroughly and made into tablets measuring 10 mm in diameter, 3 mm in thickness, and weighing 200 mg respectively.

The tablets were put to Japanese Pharmacopeia's dissolution tester in the same way as Example 3 and

it was confirmed that the tablets started foaming and breaking up into granules to disperse and suspend immediately after having been thrown into the test solution and that they kept dispersing and suspending even 8 hours later.

Example 5

80 parts by weight of methyl cellulose (viscosity of 2% aqueous solution at 20°C being 9,500 centipoises), 20 parts by weight of polyacrylic acid (viscosity of 0.2% aqueous solution pH 7.3 at 25°C being 11,500 centipoises), 40 parts by weight of sodium hydrogencarbonate, and 20 parts by weight of isoproterenol hydrochloride were mixed uniformly. Thereafter, 0.8 part by weight of magnesium stearate was added to the obtained mixture and then the admixture was made into tablets, each having 10 mmø diameter and hardness of 4 to 5 kg. The tablets were pulverized into granules ranging from 12 to 24 mesh in particle size and 150 mg of the granules were filled in No. 2 capsule. The capsule was then subjected to the dissolution test according to Japanese Pharmacopeia's test method (No. 2 method, 1st solution 500 ml, 150 rpm). About 10 minutes after the capsule was put in the test solution, the capsule case dissolved and disappeared letting the granules disperse on the surface of the test solution and continued dispersing in the form of a granular particle for 12 hours. The time required for 50% dissolution was 3.2 hours and the time required for 80% dissolution was 7.8 hours, which indicates a good sustained release performance.

Example 6

60 parts by weight of hydroxypropylmethylcellulose (viscosity of 2% aqueous solution at 20°C being 14.3 centipoises), 40 parts by weight of polyacrylic acid (viscosity of 0.2% aqueous solution pH 7.3 at 25°C being 11,500 centipoises), and 20 parts by weight of tetracycline hydrochloride were mixed together thoroughly and further 0.6 part by weight of magnesium stearate was added thereto. Tablets, each being a diameter of 10 mmø and hardness of 3 to 4 kg, were made from the mixture. The tablets were then crushed by use of a muller and granular substance ranging from 12 to 24 mesh was obtained by means of a classifier (hereunder referred to as granular substance (A)). On the other hand, 70 parts by weight of sodium hydrogencarbonate and 30 parts by weight of tartaric acid were mixed thoroughly and then 0.5 part by weight of meagnesium stearate was added thereto. The mixture was made into tablets having a diameter of 10 mmø and hardness of 3 to 4 kg. Thereafter, the tablets were crushed to give granules ranging from 12 to 24 mesh after classification. (hereunder referred to as granular substance (B)). 60 parts by weight of granule substance (A), 40 parts by weight of granular substance (B), and 0.5 part by weight of magnesium stearate were mixed uniformly and 200 mg of this mixture was filled in No. 2 capsule. The capsule was then subjected to the dissolution test according to the same method as Example 3. It was observed that the liberated granules kept dispersed and floating on the surface of the test solution for as long as 8 hours, and that it took 2.5 hours for 50% dissolution and 6.5 hours for 80% dissolution to show an excellent sustained release property.

Claims

1. An oral sustained release pharmaceutical preparation comprising, in admixture, a lower alkyl ether of cellulose, polyacrylic acid or a pharmaceutically acceptable salt thereof, a drug and an effervescent foaming agent, the amount of foaming agent ranging from 10 to 50% by weight based on the total weight of the lower alkyl ether of cellulose and polyacrylic acid or pharmaceutically acceptable salt thereof.

2. The oral sustained release pharmaceutical preparation according to claim 1, which comprises 0.1 to 1000 parts by weight of polyacrylic acid or a pharmaceutically acceptable salt thereof per 10 parts by weight of lower alkyl ether of cellulose.

3. The oral sustained release pharmaceutical preparation according to claim 1 or claim 2, wherein the preparation is in the form of a granular pilule, tablet, or capsule.

4. The oral sustained release pharmaceutical preparation according to claim 3, wherein the particle size of the granular pilule ranges from 0.5 mm to 2 mm.

5. The oral sustained release pharmaceutical preparation according to any one of the preceding claims,

wherein said drug is any of drugs for gastrointestinal diseases, drugs for the central nervous system, antiallergic agents, antihistaminic agents, drugs for the circulatory system, drugs for respiratory diseases, hormone drugs, hormone controlling drugs, drugs for urinary and genital organs, metabolic drugs, drugs for tumor, antibiotics and chemotherapeutic agents.

6. The oral sustained release pharmaceutical preparation according to any one of the preceding claims, wherein the foaming agent is present in an amount ranging from 10 to 30% by weight based on the total weight of the lower alkyl ether of cellulose and polyacrylic acid or pharmaceutically acceptable salt thereof.

7. The oral sustained release pharmaceutical preparation according to any one of the preceding claims, wherein said foaming agent is a carbonate, a bicarbonate, or a mixture of an organic acid and a carbonate or a bicarbonate.

8. The oral sustained release pharmaceutical preparation according to any one of the preceding claims, wherein the polyacrylic acid is in the form of polyacrylic acid and about 20% by weight or less of a water soluble polymer.

9. A process for producing an oral sustained release pharmaceutical preparation according to any one of the preceding claims, comprising mixing a lower alkyl ether of cellulose, polyacrylic acid or a pharmaceutically acceptable salt thereof, a drug and an effervescent foaming agent, the amount of foaming agent ranging from 10 to 50% by weight based on the total weight of the lower alkyl ether of cellulose and polyacrylic acid or pharmaceutically acceptable salt thereof.

Revendications

1. Préparation pharmaceutique retard par voie orale, comprenant, en mélange, un éther alkylique inférieur de cellulose, un poly(acide acrylique) ou l'un de ses sels pharmaceutiquement acceptable, un médicament et un agent moussant effervescent, la quantité de l'agent moussant étant comprise dans l'intervalle de 10 à 50 % en poids par rapport au poids total de l'éther alkylique inférieur de la cellulose et du poly(acide acrylique) ou de son sel pharmaceutiquement acceptable.

2. Préparation pharmaceutique retard par voie orale selon la revendication 1, qui comprend 0,1 à 1000 parties en poids de poly(acide acrylique) ou de l'un de ses sels pharmaceutiquement acceptables pour 10 parties en poids de l'éther alkylique inférieur de la cellulose.

3. Préparation pharmaceutique retard par voie orale selon la revendication 1 ou 2, qui se présente sous la forme d'une pilule granulaire, d'un comprimé ou d'une gélule.

4. Préparation pharmaceutique retard par voie orale selon la revendication 3, dans laquelle la granulométrie de la pilule granulaire est de 0,5 à 2 mm.

5. Préparation pharmaceutique retard par voie orale selon l'une quelconque des revendications précédentes, dans laquelle ledit médicament est un médicament quelconque choisi parmi les médicaments des maladies gastro-intestinales, les médicaments du système nerveux central, les agents anti-allergiques, les agents anti-histaminiques, les médicaments du système circulatoire, les médicaments des maladies respiratoires, les médicaments à base d'hormones, les médicaments régulateurs hormonaux, les médicaments des organes urinaires et génitaux, les médicaments du métabolisme, les médicaments des tumeurs, les antiblotiques et les agents chimiothérapeutiques.

6. Préparation pharmaceutique retard par voie orale selon l'une quelconque des revendications précédentes, dans laquelle l'agent moussant est présent en une quantité comprise dans l'intervalle de 10 à 30 % en poids par rapport au poids total de l'éther alkylique inférieur de la cellulose et du poly(acide acrylique) ou de l'un de ses sels pharmaceutiquement acceptable.

7. Préparation pharmaceutique retard par voie orale selon l'une quelconque des revendications précédentes, dans laquelle ledit agent moussant est un carbonate, un bicarbonate ou un mélange d'un acide organique et d'un carbonate ou d'un bicarbonate.

8. Préparation pharmaceutique retard par voie orale selon l'une quelconque des revendications précédentes, dans laquelle le poly(acide acrylique) se présente sous la forme d'un poly(acide acrylique) et d'environ 20 % en poids ou moins d'un polymère soluble dans l'eau.

9. Procédé de production d'une préparation pharmaceutique retard par voie orale selon l'une quelconque des revendications précédentes, qui consiste à mélanger un éther alkylique inférieur de la cellulose, un poly(acide acrylique) ou l'un de ses sels pharmaceutiquement acceptable, un médicament et un agent moussant effervescent, la quantité de l'agent moussant étant comprise dans l'intervalle de 10 à 50 % en poids par rapport au poids total de l'éther alkylique inférieur de la cellulose et du poly(acide acrylique) ou de son sel pharmaceutiquement acceptable.

Patentansprüche

1. Oral-Arzneizubereitung mit Retardwirkung, umfassend als Gemisch, einen Niederalkylether von Cellulose, Polyacrylsäure oder ein pharmazeutisch verträgliches Salz davon, einen Wirkstoff und ein starkes Schaummittel, wobei die Menge des Schaummittels im Bereich von 10 bis 50 Gew.-%, basierend auf dem Gesamtgewicht des Niederalkylethers von Cellulose und der Polyacrylsäure oder dem pharmazeutisch verträglichen Salz davon, liegt.

2. Oral-Arzneizubereitung mit Retardwirkung nach Anspruch 1, umfassend 0,1 bis 1000 Gew.-Teile von Polyacrylsäure oder einem pharmazeutisch verträglichen Salz davon pro 10 Gew.-Teile eines Niederalkylethers von Cellulose.

3. Oral-Arzneizubereitung mit Retardwirkung nach Anspruch 1 oder 2, worin die Zubereitung in Form einer granulären kleinen Pille, Tablette oder Kapsel ist.

4. Oral-Arzneizubereitung mit Retardwirkung nach Anspruch 3, worin die Partikelgröße der granulären kleinen Pille im Bereich von 0,5 mm bis 2 mm liegt.

5. Oral-Arzneizubereitung mit Retardwirkung nach einem der vorhergehenden Ansprüche, worin der Wirkstoff ein Wirkstoff für Magen- und Darmerkrankungen, ein Wirkstoff für das zentrale Nervensystem, ein Allergiemittel, ein Anti-Histaminmittel, ein Wirkstoff für das Blutsystem, ein Wirkstoff für Erkrankungen der Atmungswege, ein Hormonwirkstoff, ein Hormon-Kontrollwirkstoff, ein Wirkstoff für Harn- und Genitalorgane, ein Stoffwechselwirkstoff, ein Tumorwirkstoff, ein antibiotisches und chemotherapeutisches Mittel ist.

6. Oral-Arzneizubereitung mit Retardwirkung nach einem der vorhergehenden Ansprüche, worin das Schaummittel in einer Menge im Bereich von 10 bis 30 Gew.-%, basierend auf dem Gesamtgewicht des Niederalkylethers von Cellulose und der Polyacrylsäure oder dem pharmazeutisch verträglichen Salz davon, vorliegt.

7. Oral-Arzneizubereitung mit Retardwirkung nach einem der vorhergehenden Ansprüche, worin das Schaummittel ein Carbonat, ein Bicarbonat oder ein Gemisch von einer organischen Säure und einem Carbonat oder einem Bicarbonat ist.

8. Oral-Arzneizubereitung mit Retardwirkung nach einem der vorhergehenden Ansprüche, worin die Polyacrylsäure in Form von Polyacrylsäure und etwa 20 Gew.-% oder weniger eines wasserlöslichen Polymers vorliegt.

9. Verfahren zur Herstellung einer Oral-Arzneizubereitung mit Retardwirkung nach einem der vorhergehenden Ansprüche, bei dem man einen Niederalkylether von Cellulose, Polyacrylsäure oder ein pharmazeutisch verträgliches Salz davon, einen Wirkstoff und ein starkes Schaummittel mischt, wobei die Menge des Schaummittels im Bereich von 10 bis 50 Gew.-%, bezogen auf das Gesamtgewicht des Niederalkylethers von Cellulose und der Polyacrylsäure oder dem pharmazeutisch verträglichen Salz davon, liegt.

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(54) Title: NASAL DELIVERY OF APOMORPHINE

(57) Abstract: Intranasal delivery methods and compositions for the delivery of dopamine receptor agonists are provided which are effective for the amelioration of erectile dysfunction in a mammal without causing substantial intolerable adverse side effects to the mammal. Nasally administered compositions for treating male erectile dysfunction in a mammal are also provided which include a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility and/or stability.

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NASAL DELIVERY OF APOMORPHINE

BACKGROUND OF THE INVENTION

The present invention relates generally to intranasal delivery methods and dosage forms. More particularly, methods and dosage forms for the safe and reliable intranasal delivery of apomorphine to ameliorate erectile dysfunction in a mammal are provided.

Apomorphine is a potent dopamine receptor agonist which has a variety of uses. For example, it has been effectively used as an adjunctive medication in the treatment of Parkinson's disease which is complicated by motor fluctuations (T. van Laar et al., *Arch. Neurol.*, 49: 482-484 (1992)). In particular, apomorphine has been used for relieving "off-period" symptoms in Parkinson patients with such response fluctuations. In the study by van Laar et al., the intranasally applied apomorphine used to achieve the results reportedly included an aqueous solution of apomorphine hydrochloride (HCL) at a concentration of 10 mg/ml. This formulation is also used for parenteral application and is published in different Pharmacopeia's.

Also, U.S. Patent No. 5,756,483 issued to Merkus (hereinafter "the '483 patent") which is hereby incorporated by reference, discloses the intranasal delivery of a variety of compositions, including apomorphine in combination with a cyclodextrin and/or a polysaccharide and/or a sugar alcohol for treating Parkinson's disease. The '483 patent, however, discloses very narrow dosage ranges of 0.1 to 2 mg of apomorphine per nostril which is specifically tailored for the amelioration of the "off-period" symptoms of Parkinson's disease.

Further, U.S. Patent No. 5,770,606 issued to El-Rashidy et al. (hereinafter "the '606 patent"), which is hereby incorporated by reference, discloses the delivery of apomorphine in a sublingual dosage unit for alleviating psychogenic impotence or

erectile dysfunction with no substantial undesirable side effects. The '606 patent further includes results from a study conducted by the inventors on the effect of apomorphine delivered intranasally on erectile dysfunction. The study suggested that intranasal delivery of apomorphine at concentrations of 2.5 mg to 3.5 mg was effective for eliciting an erection in patients suffering from erectile dysfunction, however, since the study participants suffered extensive and serious side effects including hypotension, nausea, vomiting, impaired vision, diaphoresis and ashen coloring, it was concluded that intranasal delivery of apomorphine to treat erectile dysfunction was insufficiently safe and reliable to be a viable commercial product.

Accordingly, it is one of the purposes of this invention, among others, to provide a safe and reliable intranasal delivery system for apomorphine that ensures delivery of therapeutic amounts of the drug into the bloodstream which is fast acting, easily administered and causes no substantial adverse side effects.

SUMMARY OF THE INVENTION

It has now been discovered that this and other purposes can be achieved by the present invention, which provides for a method for ameliorating male erectile dysfunction in a mammal. This method includes the nasal administration of a dopamine receptor agonist to the mammal before, during or after sexual activity in an amount sufficient to induce an erection without inducing substantial intolerable side effects in the mammal. Preferably, the dopamine receptor agonist is apomorphine.

The present invention also provides for a pharmaceutical composition for treating male erectile dysfunction in a mammal without causing substantial intolerable adverse side effects that includes a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system. Preferably, the dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof and even further preferably, the dopamine receptor agonist is apomorphine. The chemically modified

equivalents of apomorphine preferably include a pro-drug. Further, it is preferable that apomorphine is dispersed in an aqueous or non-aqueous formulation.

In addition, the nasal delivery system of the pharmaceutical composition can include a buffer to maintain the pH of the dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant. The pharmaceutical composition can further include one or more pharmaceutical excipients and even further include a pharmaceutically acceptable preservative.

The buffer of the nasal delivery system can be selected from the group including acetate, citrate, prolamine, carbonate and phosphate buffers.

The thickening agent of the nasal delivery system can be selected from the group including methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

The humectant of the nasal delivery system can be selected from the group including sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

The present invention also provides a method of treating erectile dysfunction in a male mammal including nasally administering a pharmaceutical composition including a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system wherein the pharmaceutical composition does not cause substantial intolerable adverse side effects in the mammal.

The present invention also provides for a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein said nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when

administered to a mammal. The dopamine receptor agonist of the nasally administered pharmaceutical composition is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof. It is further preferable that chemically modified equivalents of apomorphine include a pro-drug.

The present invention also provides for a method of treating impotence and male erectile dysfunction in a human in need of such treatment including administering to a nasal membrane of the human an effective amount of a nasally administered pharmaceutical composition including a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein the nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when administered to the human.

Another preferred method of the present invention also provides for treating male erectile dysfunction in a mammal without causing substantial intolerable adverse side effects. This method includes administering into a nasal cavity of the mammal a therapeutically effective dosage of a dopamine receptor agonist in combination with a nasal delivery system. The nasal delivery system includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. The dopamine receptor agonist is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof. Preferably, chemically modified equivalents of apomorphine include a pro-drug.

Another preferred method of the present invention is a method for administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane without causing substantial intolerable adverse side effects. This method includes delivering to the nasal membrane of a mammal a dopamine receptor agonist dispersed in a nasal delivery system which includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. Preferably,

the dopamine receptor agonist is effective for the treatment of male erectile dysfunction in a mammal.

The present invention also provides for an intranasal dosage unit for treating impotency or erectile dysfunction in a mammal which does not cause substantial intolerable adverse side effects. The dosage unit includes an effective amount of a dopamine receptor agonist in combination with an intranasal carrier. The intranasal carrier includes a buffer. The buffer pH is selected to enhance absorption of the dopamine receptor agonist and to produce an erection within about 60 minutes of administering the dosage unit to a nasal mucosa of the mammal. Preferably, an erection is produced within about 45 minutes, more preferably within about 30 minutes, most preferably within about 15 minutes, and even further preferably in less than about 15 minutes.

The intranasal carrier of the intranasal dosage unit is preferably an aqueous solution. Further, the aqueous solution can be selected from the group including aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof.

Alternatively, the intranasal carrier of the intranasal dosage unit is a non-aqueous solution. The non-aqueous solution can be selected from a group including non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions and non-aqueous microemulsions and combinations thereof.

The intranasal carrier of the intranasal dosage unit can also be a combination of an aqueous solution and a non-aqueous solution.

Alternatively, the carrier of the intranasal dosage unit is a powder formulation. The powder formulation can be selected from a group including simple powder mixtures, powder microspheres, coated powder microspheres, liposomal dispersions and combinations thereof. Preferably, the powder formulation is powder

microspheres. The powder microspheres are preferably formed from various polysaccharides and celluloses selected from the group including starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carbomer, alginate polyvinyl alcohol, acacia, chitosans and combinations thereof.

The intranasal dosage unit can also include an excipient having bio-adhesive properties. Preferably, the buffer of the intranasal dosage unit is selected to have a pH of from about 3 to about 10 and more preferably from about 3.5 to 7.0.

Preferably, the intranasal dosage unit includes a humectant. A humectant can be selected from the group consisting of soothing agents, membrane conditioners, sweeteners and combinations thereof.

The present invention also provides for a nasally administered pharmaceutical composition for treating male erectile dysfunction in a mammal including a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility. The dopamine receptor agonist of this composition is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof. The system of this composition includes one of the following or combinations thereof: a glycol derivative; a sugar alcohol; glycerin; propylene glycol and glycerin; polyethylene glycol 400; ascorbic acid and water; sodium ascorbate and water; or sodium metabisulfite and water. Preferred glycol derivatives include propylene glycol and polyethylene glycol. Preferred sugar alcohols include mannitol and xylitol.

The present invention also provides for a nasally administered pharmaceutical composition for treating male erectile dysfunction in a mammal including a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its stability. The dopamine receptor agonist of this composition is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof. The system of this

composition includes one of the following or combinations thereof: a glycol derivative; a sugar alcohol; glycerin; propylene glycol and glycerin; polyethylene glycol 400; ascorbic acid and water; sodium ascorbate and water; or sodium metabisulfite and water. Preferred glycol derivatives include propylene glycol and polyethylene glycol. Preferred sugar alcohols include mannitol and xylitol.

These and other advantages of the present invention will be appreciated from the detailed description and examples which are set forth herein. The detailed description and examples enhance the understanding of the invention, but are not intended to limit the scope of the invention.

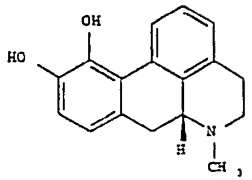
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions and methods for treating sexual dysfunction in a mammal. In particular, a method is provided for ameliorating male erectile dysfunction in a mammal by nasally administering to the mammal a therapeutically effective amount of a dopamine receptor agonist before, during or after sexual activity which is sufficient to induce an erection without causing substantial adverse side effects in the mammal.

For purposes of the present invention, the phrase "erectile dysfunction" is intended to encompass certain medically related symptoms resulting in the inability of a male to perform sexually, including penile dysfunction, as well as male impotence. As used herein, the term "impotence" is intended to mean the inability of a male to achieve and/or sustain a penile erection sufficient for vaginal penetration and intercourse.

As used herein, a "dopamine receptor agonist" is intended to encompass those members of the dopamine receptor agonist family which are able to ameliorate male erectile dysfunction when administered to a mammal. Apomorphine is an example of such a composition. Thus, the present invention is intended to encompass apomorphine and its functional equivalents including pharmaceutical salts and

chemically modified equivalents thereof, including for example pro-drug forms of apomorphine. Apomorphine can be represented by the formula:



and in the present invention can exist in a free base form or as an acid addition salt. For the purposes of the present invention, apomorphine hydrochloride is preferred; however, other pharmacologically acceptable moieties thereof can be utilized as well. The term "apomorphine" as used herein includes the free base form of this compound as well as pharmacologically acceptable acid addition salts thereof. In addition to the hydrochloride salt of apomorphine, other pharmacologically acceptable acid addition salts of apomorphine include the hydrobromide, the hydroiodide, the bisulfate, the phosphate, the acid phosphate, etc.

For the purposes of the present invention, apomorphine or a similarly acting dopamine receptor agonist is administered nasally in an amount sufficient to excite cells in the mid-brain region of the patient but without substantial adverse side effects.

This cell excitation is believed to be part of a cascade of stimulation that is likely to include neurotransmission with serotonin and oxytocin. Because dopamine receptors agonists act directly on regions of the mid-brain, the present invention also contemplates the use of such agonists for improving the sexual desire in both male and female mammals, as well as the amelioration of erectile dysfunction in males as set forth above.

The dopamine receptors in the mid-brain region of a patient can be stimulated to a degree sufficient to cause an erection by the nasal administration of apomorphine so as to maintain an adequate plasma concentration of apomorphine. The amount of

apomorphine nasally administered is an amount sufficient to cause an erection but is low enough not to cause substantial intolerable adverse side effects. As used herein, "substantial intolerable adverse side effects" include those effects caused by either the delivery system or the dopamine receptor agonist which are incompatible with the health of the user or which are so unpleasant as to discourage the continued use of the composition. Such effects include, for example, hypotension, nausea, vomiting, impaired vision, diaphoresis and ashen coloring.

Apomorphine is nasally administered about 30 to about 45 minutes prior to sexual activity, preferably about 15 to about 20 minutes prior to sexual activity, and more preferably less than 15 minutes prior to sexual activity.

The compositions according to the present invention can be administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of a composition can also include using a nasal tampon or a nasal sponge containing a composition of the present invention.

The dopamine receptor agonist can also be brought into a viscous basis via systems conventionally used, for example, natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the present compositions, many other excipients known in the art can be added such as preservatives, surfactants, co-solvents, adhesives, antioxidants, buffers, viscosity enhancing agents and agents to adjust the pH and the osmolarity.

The amount of dopamine receptor agonist administered to a patient will vary according to the delivery system used, and the age and weight of the patient. There are two critical parameters for selecting the appropriate dosage levels of the dopamine receptor agonist. First, the dosage level must be effective for achieving an erection in the patient and second, the dosage level must not cause substantial intolerable adverse side effects to the patient.

The onset of substantial intolerable adverse side effects, for example, nausea and/or vomiting, can be obviated or delayed by nasally delivering a dopamine receptor agonist at a controlled dissolution rate so as to provide circulating serum levels and mid-brain tissue levels of the dopamine receptor agonist sufficient for an erection and without inducing nausea and/or vomiting. When it is necessary to administer higher doses of a dopamine receptor agonist, for example, doses above about 2 mg, the likelihood of a substantial intolerable adverse side effect onset can be reduced by concurrently administering a ganglionic agent capable of inhibiting the ganglionic response, for example, nicotine or lobeline sulfate.

Other antiemetic agents that can be used in accordance with the present invention include metoclopramide; phenothiazines such as chlorpromazine, prochlorperazine, pipamazine, thiethylperazine and oxypendyl hydrochloride; serotonin (5-hydroxytryptamine or 5-HT) agonists such as domperidone, odansetron and histamine antagonists including buclizine hydrochloride, cyclizine hydrochloride and dimenhydrinate; parasympathetic depressants such as scopolamine; metopimazine; trimethobenzamide; benzquinamine hydrochloride; and diphenidol hydrochloride.

As set forth previously, the nasal delivery systems that can be used with the present invention can take various forms including aqueous solutions, non-aqueous solutions and combinations thereof. Aqueous solutions include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous solutions include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

The various forms of the delivery system set forth above can include a buffer to maintain the pH of the dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant. Desirably, the pH of the buffer is selected to

maintain the dopamine receptor agonist in a non-ionized form. In particular, the pH of the buffer is selected to optimize the absorption of the dopamine receptor agonist across the nasal mucosa. The particular pH of the buffer, of course, can vary depending upon the particular nasal delivery formulation as well as the specific dopamine receptor agonist composition selected. Buffers that are suitable for use in the present invention include acetate, citrate, prolamine, carbonate and phosphate buffers.

With respect to the non-aqueous formulations set forth above, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa.

In the present invention, the pH of the compositions should be maintained from about 3.0 to about 10.0. Compositions having a pH of less than about 3.0 or greater than about 10.0 can increase the risk of irritating the nasal mucosa of a recipient. Further, it is preferable that the pH of the compositions be maintained from about 3.0 to about 7.0.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation discussed above.

The compositions of the present invention can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used in the present invention include sorbitol, mineral

oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and combinations thereof. The concentration of the humectant in the present compositions will vary depending upon the agent selected.

In the present invention, other optional ingredients can also be incorporated into the nasal delivery system provided that they do not interfere with the action of the dopamine receptor agonist or significantly decrease the absorption of the dopamine receptor agonist across the nasal mucosa. Such ingredients include pharmaceutically acceptable excipients and preservatives.

To extend shelf life, preservatives can be added to the present compositions. Suitable preservatives that can be used with the present compositions include benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium chloride and preferably benzalkonium chloride is used. Typically, the preservative will be present in a composition in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

The present invention provides for the compositions as described above which are administered nasally to a mammal to treat erectile dysfunction. For purposes of the present invention, "administered nasally" or "nasal administration" is intended to mean that the dopamine receptor agonists are combined with a suitable delivery system for absorption across the nasal mucosa of a mammal, preferably, a human.

A preferred embodiment of the present invention provides for a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain the pH of the agonist, a pharmaceutically acceptable thickening agent and a humectant. As used herein, "therapeutically effective amount" means a unit dosage of the present dopamine receptor agonist which is able to be combined with a pharmaceutically acceptable nasal delivery system and absorbed through the nasal mucosa of a mammal

to produce an erection in about 1 hour, preferably in about 45 minutes, more preferably in about 30 minutes, and most preferably in 15 minutes or less which renders the intended physiological effect which is to induce a penile erection in a mammal with penile erectile dysfunction without causing substantial intolerable adverse side effects to the mammal. Preferably, the dopamine receptor agonist is selected from a group including apomorphine, chemically modified equivalents which include a pro-drug and pharmaceutical salts thereof.

Another preferred embodiment of the present invention provides for a method of treating impotence and male erectile dysfunction in a human in need of such a treatment. This method includes administering into a nasal cavity of a mammal for absorption through the nasal mucosa thereof a therapeutically effective dosage of a dopamine receptor agonist as previously set forth in combination with a nasal delivery system. The dopamine receptor agonist is preferably selected from a group including apomorphine, chemically modified equivalents which include a pro-drug and pharmaceutical salts thereof. For purposes of the present invention, the nasal delivery system can include a pharmaceutically acceptable buffer, a thickening agent and a humectant.

In another preferred embodiment of the present invention, a method is provided for administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane without causing substantial intolerable adverse side effects in the mammal. This method includes delivering to a nasal membrane of a mammal a dopamine receptor agonist which is dispersed in a nasal delivery system that includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. In this method, the dopamine receptor agonist is effective for the treatment of a sexual dysfunction in a mammal, particularly impotence and/or erectile dysfunction in a male mammal.

Another preferred embodiment of the present invention provides for an intranasal dosage unit for treating impotency in a mammal and which does not cause

substantial intolerable adverse side effects in the mammal. The intranasal dosage unit includes an effective amount of a dopamine receptor agonist in combination with a pharmaceutically acceptable intranasal carrier. This carrier includes a buffer. The pH of the buffer is selected as set forth above to facilitate dopamine receptor agonist absorption through the nasal mucosa so an erection is achieved in about 60 minutes, preferably in about 45 minutes, more preferably in about 30 minutes and most preferably in 15 minutes or less after administration.

The following examples are provided to assist in further understanding the invention. The particular materials and conditions employed are intended to be further illustrative of the invention and are not limiting upon the reasonable scope thereof.

A series of experiments were performed to illustrate features and advantages of the present invention. Several conditions were common to each experiment. For example, in Examples 1-4, apomorphine was administered to healthy male subjects who did not suffer from erectile dysfunction. Further, none of the subjects took any medication for two weeks prior to these experiments.

The following examples show that apomorphine can be nasally administered without causing substantial intolerable adverse effects. A different dosage of apomorphine was administered in each experiment to determine a preferred range of dosages having minimal adverse effects.

EXAMPLE 1

TABLE 1 shows the results of an experiment in which 1.0 mg of apomorphine HCL was nasally administered to nine male subjects.

TABLE 1

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	2	0	0	0	0	2
Sneezing	1	0	1	0	0	2
Unusual Taste	2	0	0	0	0	2
Nausea	1	1	0	0	0	2
Tearing of Eyes	1	0	0	0	0	1
Lightheadedness	1	0	0	0	0	1
Tiredness	3	0	0	0	0	3
Congestion	1	0	0	0	0	1
Sweating	1	0	0	0	0	1

It should be noted that some of the subjects of this experiment suffered from more than one symptom and one subject did not suffer from any symptoms.

As shown in TABLE 1, the symptoms suffered by the subjects in this experiment were generally not troublesome and of very short duration. One subject, though, suffered from moderate sneezing and another subject suffered from mild to moderate nausea. The adverse effects with nasal administration of 1.0 mg of

apomorphine HCL were minimal and the severity of the adverse effects were generally not troublesome.

EXAMPLE 2

TABLE 2 shows the results of an experiment in which 0.5 mg of apomorphine HCL was nasally administered to three male subjects.

TABLE 2

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	2	0	0	0	0	2
Nasal Pain	1	0	0	0	0	1
Unusual Taste	1	0	0	0	0	1

One of the subjects of this experiment did not suffer any symptoms and two of the three subjects in this experiment suffered mild symptoms which were not troublesome and were of very short duration. The results of this experiment show minimal adverse effects with nasal administration of 0.5 mg of apomorphine HCL.

The results of this experiment also show that nasal administration of apomorphine HCL was effective for inducing an erection. In particular, one of the three subjects experienced an erection while another felt the beginning of an erection.

EXAMPLE 3

TABLE 3 shows the results of an experiment in which 2.0 mg of apomorphine HCL was nasally administered to nine male subjects.

TABLE 3

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	1	0	0	0	0	1
Sneezing	0	1	0	0	0	1
Unusual Taste	4	0	0	0	0	4
Nausea	3	0	0	0	0	3
Lightheadedness	2	0	0	0	0	2

It should be noted that some of the subjects of this experiment suffered from more than one symptom and one subject did not suffer from any symptoms.

Eight of the nine subjects in this experiment suffered from symptoms of mild degree as shown in TABLE 3. Further, the symptoms suffered by all of the subjects were not troublesome. The results of this experiment show very minimal adverse effects with nasal administration of 2.0 mg of apomorphine HCL.

The results of this experiment also show that nasal administration of apomorphine HCL was effective for inducing an erection. In particular, three of the nine subjects of this experiment had a partial erection while one subject felt an erection.

EXAMPLE 4

TABLE 4 shows the results of an experiment in which 4.0 mg of apomorphine HCL was nasally administered to two male subjects.

TABLE 4

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or or very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Sneezing	0	0	0	1	0	1
Nausea	0	1	0	0	0	1
Lightheadedness	0	1	0	0	0	1

One subject of this experiment did not suffer any symptoms while the other subject experienced mild to moderate nausea and lightheadedness, which were not troublesome and were of very short duration, and moderate sneezing, which was somewhat troublesome. In particular, this subject felt like vomiting, felt lightheaded for twenty minutes after apomorphine was administered and sneezed four times. It is known in the art that the emetic effect of high dosages of apomorphine includes vomiting and therefore, it is believed that this subject suffered these symptoms due to the higher dosage of apomorphine.

The results of this experiment do not show substantial adverse effects with nasal administration of 4.0 mg of apomorphine HCL.

Examples 1-4 show that apomorphine can be nasally administered at different dosages without substantial adverse effects and further, adverse effects are minimal with a dosage of apomorphine of equal to or less than 2.0 mg.

EXAMPLE 5

TABLE 5 shows the solubility and stability of apomorphine hydrochloride dispersed in several different systems.

TABLE 5

System #	Composition of System	pH	Solubility (mg/mL)	Solubility Enhancement %	Improved Stability *
1	Water	3.6	20.9	-	-
2	Propylene Glycol	--	84.5	304.3	Yes
3	Glycerin	--	37.4	78.9	Yes
4	50% Propylene Glycol + 50% Glycerin	--	67.9	224.9	Yes
5	Polyethylene Glycol 400	--	19.9	None	Yes
6	1.8% Ascorbic Acid + 98.2% Water	2.3	25.0 - 30.0	19.6 - 43.5	Yes
7	0.2% Sodium Ascorbate + 99.8% Water	5.0	20.0 - 25.0	0 - 19.6	Yes
8	0.5% Sodium Metabisulfite + 99.5% Water	3.1	249	19.1	Yes

* Based on color change.

TABLE 5 shows the composition of several systems in which apomorphine HCL has been dispersed. System #1 includes water and served as a control for comparison with System #2 - System #8. TABLE 5 also shows the solubility of apomorphine HCL after it has been dispersed in the above systems. It also shows that the stability of apomorphine HCL has been improved after it has been dispersed in the above systems. The improved stability of apomorphine HCL was determined based on the color change of apomorphine HCL. For instance, a reduced degree of color

formation after dispersion of apomorphine HCL in a system would signify improved stability.

As shown in TABLE 5, the solubility of apomorphine HCL clearly improves significantly when it is dispersed in the compositions of System #2 - System #4. Further, the solubility of apomorphine HCL improved moderately when it was dispersed in the compositions of System #6 - System #8.

Apomorphine HCL exhibited improved stability when dispersed in each of System #2 - System #8.

The results of this experiment demonstrate that a pharmaceutical composition according to the present invention and including apomorphine dispersed in different systems as shown above, can improve the solubility and stability of apomorphine.

Thus, while there have been described what are presently believed to be the preferred embodiments of the present invention, those skilled in the art will realize that other and further embodiments can be made without departing from the spirit and scope of the invention, and it is intended to include all such further modifications and changes as come within the true scope of the claims set forth herein.

WHAT IS CLAIMED IS:

1. A method of ameliorating male erectile dysfunction in a mammal comprising nasally administering a therapeutically effective amount of a dopamine receptor agonist to said mammal before, during or after sexual activity which is sufficient to induce an erection without causing substantial intolerable adverse side effects to said mammal.

2. The method of Claim 1, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

3. A pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system, wherein said pharmaceutical composition does not cause substantial intolerable adverse side effects in said mammal.

4. The pharmaceutical composition of Claim 3, wherein said dopamine receptor agonist is apomorphine.

5. The pharmaceutical composition of Claim 4, wherein said apomorphine is dispersed in an aqueous or non-aqueous formulation.

6. The pharmaceutical composition of Claim 4, wherein said nasal delivery system comprises a buffer to maintain the pH of said dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant.

7. The pharmaceutical composition of Claim 6, further comprising one or more pharmaceutical excipients.

8. The pharmaceutical composition of Claim 7, further comprising a pharmaceutically acceptable preservative.

9. The pharmaceutical composition of Claim 6, wherein said buffer is selected from the group consisting of acetate, citrate, prolamine, carbonate and phosphate buffers.

10. The pharmaceutical composition of Claim 6, wherein said thickening agent is selected from the group consisting of methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

11. The pharmaceutical composition of Claim 6, wherein said humectant is selected from the group consisting of sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

12. A method of treating erectile dysfunction in a male mammal comprising nasally administering the composition according to Claim 3.

13. The pharmaceutical composition of Claim 3, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

14. The pharmaceutical composition of Claim 13, wherein said chemically modified equivalents comprise a pro-drug.

15. A nasally administered pharmaceutical composition comprising a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein said nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when administered to said mammal.

16. The nasally administered pharmaceutical composition of Claim 15, wherein said dopamine receptor agonist is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

17. The nasally administered pharmaceutical composition of Claim 16, wherein said chemically modified equivalents comprise a pro-drug.

18. A method of treating impotence and male erectile dysfunction in a human in need of such treatment comprising administering to a nasal membrane of said human an effective amount of a composition according to Claim 15.

19. A method of treating sexual dysfunction without causing substantial intolerable adverse side effects in a mammal comprising administering into a nasal cavity of said mammal a therapeutically effective dosage of a dopamine receptor agonist in combination with a nasal delivery system comprising a pharmaceutically acceptable buffer, a thickening agent and a humectant.

20. The method of Claim 19, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

21. The method of Claim 20, wherein said chemically modified equivalents comprise a pro-drug.

22. A method of administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane thereof comprising delivering to said nasal membrane a therapeutically effective amount of said dopamine receptor agonist which does not cause substantial intolerable adverse side effects in said mammal, wherein said dopamine receptor agonist is dispersed in a nasal delivery system comprising a pharmaceutically acceptable a buffer, a thickening agent and a humectant.

23. The method of Claim 22, wherein said dopamine receptor agonist is effective for the treatment of male erectile dysfunction in a mammal.

24. An intranasal dosage unit for treating impotency or erectile dysfunction in a mammal comprising an effective amount of a dopamine receptor agonist in combination with an intranasal carrier comprising a buffer, wherein said dosage unit does not cause substantial intolerable adverse side effects in said mammal and an erection is produced in said mammal within about 60 minutes of administering said dosage unit to a nasal mucosa of said mammal.

25. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 45 minutes.

26. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 30 minutes.

27. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 15 minutes.

28. The intranasal dosage unit of Claim 24, wherein said erection is produced in less than about 15 minutes.

29. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is an aqueous solution.

30. The intranasal dosage unit of Claim 29, wherein said aqueous solution is selected from the group consisting of aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof.

31. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is a non-aqueous solution.

32. The intranasal dosage unit of Claim 31, wherein said non-aqueous solution is selected from the group consisting of non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

33. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is a powder formulation.

34. The intranasal dosage unit of Claim 33, wherein said powder formulation is selected from the group consisting of simple powder mixtures, powder microspheres, coated powder microspheres, ribosomes and combinations thereof.

35. The intranasal dosage unit of Claim 24, further comprising an excipient having bio-adhesive properties.

36. The intranasal dosage unit of Claim 24, wherein said buffer is selected to have a pH of from about 3 to about 10.

37. The intranasal dosage unit of Claim 24, further comprising a humectant.

38. The intranasal dosage unit of Claim 37, wherein said humectant is selected from the group consisting of soothing agents, membrane conditioners, sweeteners and combinations thereof.

39. A nasally administered pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility.

40. The nasally administered pharmaceutical composition of Claim 39, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

41. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises glycerin.

42. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises a glycol derivative.

43. The nasally administered pharmaceutical composition of Claim 42, wherein said glycol derivative is propylene glycol.

44. The nasally administered pharmaceutical composition of Claim 42, wherein said glycol derivative is polyethylene glycol.

45. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises a sugar alcohol.

46. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises propylene glycol and glycerin.

47. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises ascorbic acid and water.

48. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises sodium ascorbate and water.

49. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises sodium metabisulfite and water.

50. A nasally administered pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its stability.

51. The nasally administered pharmaceutical composition of Claim 50, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

52. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises glycerin.

53. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises a glycol derivative.

54. The nasally administered pharmaceutical composition of Claim 53, wherein said glycol derivative is propylene glycol.

55. The nasally administered pharmaceutical composition of Claim 53, wherein said glycol derivative is polyethylene glycol.

56. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises a sugar alcohol.

57. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises propylene glycol and glycerin.

58. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises polyethylene glycol 400.

59. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises ascorbic acid and water.

60. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises sodium ascorbate and water.

61. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises sodium metabisulfite and water.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04268

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/44
US CL : 514/284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, CAPLUS, BIOSIS
search terms: apomorphine, nasal, erectile, dopamine, buffer.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,756,483 A (MERKUS) 26 May 1998, entire document.	1-61
Y	US 5,770,606 A (EL-RASHIDY et al.) 23 June 1998, entire document	1-61
Y	WO 99/27905 A (DANBIOSYST UK LIMITED) 10 June 1999, entire document	1-61
Y,P	WO 99/66933 A (NEW MILLENNIUM PHARMACEUTICAL RESEARCH INC.) 29 December 1999, entire document	1-61

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Shengjun Wang Telephone No. (703) 308-1235

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